

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TRIADIMENOL

Chemical Code # 2307, Tolerance # 50512

Original date: 4/18/90

Revised date: 6/7/00

I. DATA GAP STATUS

Combined, rat:	No data gap; no adverse effect
Chronic toxicity, dog:	No data gap; no adverse effect
Oncogenicity, mouse:	No data gap; no adverse effect
Reproduction, rat:	No data gap; no adverse effect
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No data gap; no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 172555 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T000607

Duncan, 6/7/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

SB 950-MANDATED STUDIES

Combined, Rat

005, 037; 014079, 129715; "KWG 0519 [Triadimenol, the active ingredient of Baytan*]: Chronic toxicity study on rats (2-Year feeding experiment)" (F. Krotlinger, et. al., Bayer AG, Wuppertal, Germany, 7/15/82 (original), 3/14/94 (supplement); KWG 0519 Technical (94.9% purity); Sixty rats/group at dosages of 0, 125, 500, and 2000 ppm for 24-month duration. NOEL = 125 ppm (modest increases in SGOT and/or SGPT in 500 ppm males or females). At 2000 ppm, these enzyme activities were more markedly and consistently elevated, especially in males; and relative liver weights were increased in females. There were no microscopic indications of liver pathology at any dose level. Body weights of 2,000 ppm rats of both sexes were consistently less than control values. There was a slight reduction from control levels in RBC counts of 2,000 ppm females, and a slight increase in blood urea nitrogen levels was noted in 2,000 ppm males and females; however there was little or no evidence of treatment effects on blood forming organs or kidneys. Study was originally unacceptable but subsequently upgraded with additional data concerning test article and dosing material; **acceptable; No adverse effect; (Aldous, 3/22/90; upgraded, Leung, 11/21/94).

023 070976 Historical data relevant to study 50512-005:014079, above. (No worksheet needed, as these data do not impact study evaluation).

Chronic Toxicity, Rat

See under Combined Rat above.

Chronic Toxicity, Dog

011, 013, 037; 14124, 129714; "KWG 0519 (c.n. Triadimenol): First chronic study of toxicity to dogs on oral administration. (Two-year feeding study)". (K. Hoffmann, et. al., Bayer AG, Wuppertal, Germany; 10/5/84 (Original), 3/14/94 (Supplement); Four beagles/sex/group at dosages of 0, 150, 600, or 2400 ppm KWG 0519 (Triadimenol, 94.9% purity) for 2 years. **No adverse effects were indicated. The NOEL for females was 150 ppm (based on decreased body weight and increased N-demethylase activity). There was no NOEL for males (body weights were statistically significantly reduced ($p < 0.05$) in high and low treatment groups compared to controls). Data support a NOAEL of 600 ppm for either sex, in the absence of any truly "adverse" effects; based on a combination of several parameters which appeared to be affected at 2400 ppm (weight gain decrements in both sexes; adaptive metabolic changes, particularly increased N-demethylase activity in high dose males and females; and increased alkaline phosphatase levels in males). Study was originally unacceptable but subsequently upgraded with additional data clarifying the amounts of the test article in the test diets; **acceptable;** (Aldous, 3/30/90; upgraded, Leung, 11/21/94).

025 067949 This is an expanded analysis of historical control beagle body weight gain data

relevant to dog study 50512-011, 013:014124. The mean weight gain data (including standard deviations) for 1 and 2-year intervals for males and females had been given in the final report. This supplement provides individual dog body weight data within each of the 30 chronic studies, at 1 and 2-year time points. These are potentially useful data, however the CDFA review had recommended a NOAEL based on criteria other than body weight changes; therefore this detailed historical body weight analysis does not indicate a change in the CDFA review. Aldous (no additional worksheet), 4/10/90.

013 025347 "KWG 0519 (c.n. triadimenol): Second chronic study of toxicity to dogs on oral administration (Six-month feeding study)". This study was conducted to provide a "NOEL" for chronic dog studies. Dosages of 0, 10, 30, or 100 ppm KWG 0519 were administered to groups of 6 beagles/sex/group for 6 months. There were no effects on body weight, and no other treatment effects noted in the limited evaluations conducted. This study suggests that an appropriate NOEL for record No. 014124, above, should be 100 ppm. Useful information. No CDFA worksheet, since this study was not critical to CDFA in establishing a NOAEL for the chronic dog study. Aldous, 3/30/90.

005 014078 [A study on a related test compound, triadimefon (Bayleton*). See CDFA review for 410-002:980101.]

Oncogenicity, Rat

See under Combined Rat above.

Oncogenicity, Mouse

004 014064 "KWG 0519 (Triadimenol, Baytan* active ingredient): Chronic toxicological study on mice (Feeding experiment over two years)". In-life phase presumably done at Bayer AG, Institute of Toxicology, Wuppertal, 4/29/82. Fifty mice/group at doses of 0, 125, 500, and 2000 ppm, strain CF₁ W74, were maintained for 2 years. **Unacceptable study**: design problems included failure to systematically examine several major tissues or organs. Major husbandry problems included frequent failure to collect tissues, or unacceptable frequency of autolysis of tissues submitted for evaluation. Other deficiencies were indicated in the review. The study was too poorly conducted to properly assess NOELs. An apparent NOAEL of 125 ppm might be assigned (based on body weight decrements in males, and on SGOT elevations in females). A **possible adverse effect** was adenomas in livers of females (incidence of 0, 0, 4, and 6 in increasing dosage groups). Aldous, 3/19/90. NOTE: Historical tumor control data in 023:070975 may be relevant for evaluation of hepatocellular tumor results.

025 067950 "Chronic toxicological study on mice, Mobay Report No. 82291/1508. Evaluation of liver tissues from female mice. Pathology Report." This is a second evaluation of liver slides from mouse oncogenicity study, 50512-004:014064. This evaluation was conducted by Experimental Pathology Laboratories, Inc., Research Triangle Park, NC. on behalf of Mobay Chemical Corp. Date of the re-evaluation was 3/23/88. The re-evaluation confirmed the overall results of the original investigators, that an increase in hepatocellular tumors had occurred in females at the two highest dosages. The status of the study is unchanged. Incidence tables are in CDFA worksheet. Aldous, 4/10/90.

023 070975 Historical control data for 50512-004:014064, above. These data show one out

of 13 studies with control hepatocellular adenoma incidence of 6/50 (comparable to original pathologist's count in the cited study). Mean female control hepatocellular adenoma incidence was 3.6% (about 2/50).

Thus the tumor type was not uncommon, and the referenced study outcome would be found not significant or marginally significant, depending on the statistical tests applied. No change in study status. No separate worksheet. Aldous, 4/12/90.

045; 172555; "KWG 0519 / Oncogenicity Study in CD-1 Mice (Dietary Administration Over 18 Months" (L. Schladt; Bayer AG, Department of Toxicology, Wuppertal, Germany; Bayer AG Study No. T4060738, Report No. 108689; 12/9/98); Triadimenol (KWG 0519 (Batch No. 816176225, 96.8-97.6%) administered in the diet at dose levels of 0, 80, 400, and 2000 ppm (males: 0, 11.3, 60.2, 340.3 mg/kg/day; females: 0, 17.2, 91.3, 472.9 mg/kg/day) for 80 weeks; 50 Crl:CD-1(ICR)BR mice/sex/dose level; reduced body weight (w/ slightly increased food consumption) was observed in 400 ppm males (up to 7% less than control), 2000 ppm males (up to 21% less than control), and 2000 ppm females (up to 16% less than control); relative liver weight was increased 13% in 400 ppm males, 48% in 2000 ppm males, and 27% in 2000 ppm females; liver histopathology included hepatocellular hypertrophy, fatty change (females only), hepatocellular vacuolation (females only), and single cell necrosis; there was **no indication of an oncogenic effect; Chronic NOEL = 80 ppm in males, 400 ppm in females (based on increased liver weights and liver histopathology). **Acceptable.** (Duncan, 5/30/00)

Reproduction, Rat

013, 037; 25346, 129712; "KWG 0519 (proposed c.n. triadimenol): Generation study on rats". (E. Loser, et. al., Bayer AG, Wuppertal, Germany, 1/23/84 (Original), 3/14/94 (Supplement); Ten males and 20 females per group in a 2-generation, 2 litters/generation design. Wistar rats received 0, 20, 100, or 500 ppm triadimenol (batch no. 816066128; 97.5% purity) in diets on a continuous basis. **No adverse effects; The apparent NOEL was 100 ppm [diminished birth weights and weights at weaning of 500 ppm F1b offspring (these changes were not observed at other mating trials): also diminished body weights (associated with reduced food consumption) during the growth phase of 500 ppm F1b rats]. Study was originally unacceptable and subsequently upgraded with additional data regarding dose level justification, analysis and description of test diets; **acceptable**; (Aldous, 4/5/90; upgraded, Leung, 11/21/94).

005 014077 [A study on a related test compound, triadimefon (Bayleton*). See CDFA review for 410-002:980115.]

Teratology, Rat

** 031; 086886; "Developmental Toxicity Study in the Rat with Baytan Technical", (Miles, Inc., Elkhart, IN, Report No. MTD0156, May 8, 1990); Baytan technical (Batch # 6-03-0140, 95% Triadimenol) administered by oral gavage at dosages of 0 (Aqueous Carboxymethylcellulose/Tween 80), 5, 15, 25, and 60 mg/kg on days 6 - 15 of gestation to 28 female Charles River Crl:CD BR rats per dose; **No adverse effects**; maternal NOEL = 25 mg/kg (decreased body weight gain, increased placental weight), Developmental NOEL = 15 mg/kg (increased extra ribs), Developmental NOAEL > 60 mg/kg; **acceptable**; (DiBiasio and Chernoff, 7/19/90).

**024 070979 "Embryotoxicity (including teratogenicity) study with KWG 0519 in the rat".

Research and Consulting Co., AG, 2/2/87. 25 Wistar rats/group were gavaged on days 6-15 p.c. with 0, 30, 60, or 120 mg/kg/day KWG 0519 in 0.5% aq. Cremophor EL. **Maternal NOEL** = 30 mg/kg/day (decreased body weights and decreased food consumption during treatment period). **Developmental NOEL** = 30 mg/kg/day (increased incidence of bilateral 14th ribs). The **NOAEL for developmental effects** = 60 mg/kg/day, based on a small increase in embryonic resorptions at 120 mg/kg/day. **Acceptable. No adverse effects** (a developmental change with no impact on viability of offspring and a relatively high NOEL was observed at a dose level which elicited minor maternal toxicity). Aldous, 4/10/90. [NOTE: Increased incidence of 14th rib was also seen in a rat teratology study for the congener, triadimefon: see 00410-013:980105, a study conducted by St. Marianna Univ. School of Medicine, Kawasaki, Japan, on 3/13/81.]

024 070980 "Dose-finding embryotoxicity (including teratogenicity) study with KWG 0519 in the rat" (RCC AG Report No. 94761, April 30, 1986). Pilot study for 50512-024 070979 (above). Five dams/group dosed up to 150 mg/kg/day from days 6-15 p.c. The latter dose reduced maternal food consumption and maternal body weight gain, and led to a 42% incidence of embryonic resorptions. No separate CDFA worksheet for this pilot study, but this study was considered in the 4/10/90 CDFA review, above.

016 075765 Supplemental information provided to EPA regarding rat teratology study 50512-024:070979, above. Data are a summary and statistical analysis of supernumerary rib data. Fetal or litter incidences of unilateral or bilateral 14th ribs were statistically significant in 60 and 120 mg/kg/day groups. 14th ribs were always rudimentary in this study. New data are useful, but do not change status of study, since the NOEL for 14th ribs had already been placed at 30 mg/kg/day, and the NOAEL for the study was based on embryonic resorptions. Aldous, 4/10/90 (no worksheet).

005 014076 "KWG 0519: Evaluation for embryotoxic and teratogenic effects on orally dosed rats". Bayer AG, Institute of Toxicology, Wuppertal, Oct. 7, 1977. Twenty pregnant rats/group, with doses of 0, 10, 30, and 100 mg/kg/day by gavage on days 6-15. **No adverse effects indicated:** apparent maternal NOEL 30 mg/kg/day (weight gain decrement); apparent developmental NOEL = 30 mg/kg/day (bone alterations, sternum). **Unacceptable, upgradeable:** specific information about test article, dosing suspensions, maternal body weight data, and fetal bone alteration data were requested in the CDFA review. Aldous, 3/27/90.

013 025345 "KWG 0519 (common name: Triadimenol) Study for embryotoxic effects on rats after oral administration". Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, 5/17/84. A low dosage range teratology study. **No adverse effects indicated.** No further information is necessary on this study, since there is a more rigorous study available. **Unacceptable, not upgradeable.** Aldous, 4/5/90.

Teratology, Rabbit

024 059733 "Embryotoxicity (including teratogenicity) study with KWG 0519 in the rabbit". RCC, Umweltchemie AG, 7/24/87. Doses of 0, 8, 40, and 200 mg/kg/day KWG 0519 (Triadimenol, 97%) on days 6-18 p.c.; to 16 mated Chinchilla rabbits per group. **Maternal NOEL = 40 mg/kg/day

(significantly reduced body weights, associated with marked reduction in food consumption during treatment. Food consumption was significantly elevated in high dose dams following termination of treatment. High dose dams were excited or irritable, and frequently had hair loss and sores on skin, which were presumed to be self-inflicted). **Developmental NOEL** = 40 mg/kg/day [small (non-significant) increase in early postimplantation losses, small (non-significant) decrease in mean fetal weights, increased ($p < 0.01$) incidence of minor skeletal anomalies]. **Acceptable, No adverse effects:** The possibly treatment-related developmental findings were observed in the presence of marked maternal toxicity, and are likely to have resulted from such toxicity. In any case, there was a comparatively high NOEL for developmental effects. Aldous, 4/6/90.

022 090040 Supplement to 50512-024:059733, above. Skeletal examination summary data were provided on both "per-fetus" and on "per-litter" basis, with statistical significance noted where applicable. Most statistically significant findings appeared to be random, however the frequencies of non-ossification of the medial phalanx of the fifth digits of the forelimbs were consistently statistically significantly elevated in high dose fetuses. The same applied to the frequencies of non-ossification of the medial phalanges of the fourth toe. These trends are consistent with a slight delay in development manifest by slightly reduced mean pup weights in the primary study. These data were examined in conjunction with review of the final report (no separate worksheet). Aldous, 4/6/90.

016 075766 A statistical analysis intended as a supplement to 50512-024:059733. This supplementary analysis had errors (dosage levels as presented came from a parallel study). The corrected analysis is found in 50512-022:090040, above. Aldous, 4/10/90 (no separate worksheet).

024 070978 Dose-finding study for 50512-024:059733, above. A dose of 300 mg/kg/day was clearly intolerable. The range selected for the primary study are justifiable, based on this study. Aldous (no worksheet), 4/6/90.

005 014075 "REPROTOX-Order Number 494: Study No. KWG 0519/019: Embryotoxicity of KWG 0519 in rabbits". REPROTOX GmbH (Huntingdon Research Centre, Deutschland), Oct. 15, 1980 (signoff by QAU). Eleven to 13 NZW rabbits/group were dosed by gavage (aqueous Cremophor EL suspension) with 0, 10, 30, or 100 mg/kg/day of KWG 0519 from days 6-18 p.c. **No adverse effects were indicated:** Maternal NOEL = 30 mg/kg/day (slight decrement in body weight gain during treatment period); Developmental NOEL = 30 mg/kg/day (slight reduction in fetal weights). Study is **not acceptable, but upgradeable** (specific questions about test article and dosing solution need to be addressed). Aldous, 3/28/90.

035; 116556; "A Developmental Toxicity Study in Rabbits with Baytan Technical"(Author: G.R. Clemens et. al.; Miles Inc., Toxicology Department, Elkhart, IN; Report No. 102692; 6/9/92); Baytan (Batch No. PF8741; 96.0% triadimenol); 0, 5, 25, 125 mg/kg oral gavage; 20 New Zealand White SPF female rabbits/dose level; no maternal mortality or clinical signs of toxicology; decreased body weight, feed consumption and fecal output observed at high dose; no adverse effects on maternal reproductive or fetal developmental parameters; maternal NOEL = 25 mg/kg (based on decreased body weight and feed consumption); developmental NOEL = 125 mg/kg (based on no adverse affects); **Acceptable.** (Miller,

7/12/93)

Gene Mutation

** 005 014069 "Mutagenicity Evaluation of KWG 0519 in the Mouse Lymphoma Forward Mutation Assay: Final Report." (Litton Bionetics, Inc., Kensington, Maryland, June, 1982, LBI Project 20999, Mobay No. 82353) KWG 0519, Batch 816 066 128, 97.5%, white powder; tested with mouse lymphoma L5178Y TK+/- with and without Aroclor 1254-induced male Sprague-Dawley rat liver activation. Nonactivation concentrations: Trial 1 of 0 (solvent and untreated control), 7.8, 15.6, 31.3, 62.5 and 125 ug/ml and Trial 2 of 0, 25, 37.5, 50, 75, 100 and 150 ug/ml. Activation concentrations: Trial 1 of 0, 3.9, 7.8, 15.6, 31.3 and 62.5 ug/ml and Trial 2 of 0, 25, 37.5, 50, 75, 100 and 150 ug/ml. Positive controls of ethylmethane sulfonate without activation and dimethylnitrosamine with activation. **No evidence of an increase in forward mutations. Acceptable.** Gee, 4/16/90.

005 014073 "KWG 0519: Mutagenicity Test on Bacterial System." (Nagane, M., J. Hatanaka and A. Iyatomi, Nihon Tokushu Noyaku Seizo K. K., Agricultural Chemicals Institute, Toxicological Laboratory, 3/29/82) Triadimenol, 97.5%; tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and with Escherichia coli B/r try⁻ hcr⁻; with and without activation with PCB-induced rat liver S9; overnight bacterial cultures used for testing; 20 minute preincubation before plating; duplicate plates, single trial. Concentrations tested were 0, 5, 10, 100, 500, 1000 or 5000 ug/plate with 5000 ug/plate being toxic. **No adverse effect reported. Unacceptable, not upgradeable** (only duplicate plates, single trial, no QA) Gee, 4/13/90.

005 014074 "KWG 0519: Salmonella/Microsome Test for Detection of Point-Mutagenic Effects." (Herbold, B, Bayer AG, institut fuer Toxikologie, FGR, 2/16/79, Study No. KWG 0519/008) Triadimenol, 93.7%; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 at 0 (DMSO), 4, 20, 100, 500 or 2500 ug/plate, 4 plates per concentration, single trial; with and without S-9 prepared from Aroclor 1254-induced male Sprague-Dawley rat liver; cytotoxicity at 2500 mg/plate based on duplicate plates for cell count; **no evidence for increase in reversion rate. Unacceptable** (no individual plate counts, use of a 24-hour culture of bacteria, marginal response of positive controls). Gee, 4/13/90.

006 014080 "Triadimenol Microbial Mutagenicity Study." (Tanahashi, N. and M. Moriya, Department of Toxicology, Institute of Environmental Toxicology, Japan, 12/3/82) Triadimenol, 97.5%; tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and with Escherichia coli strain WP2 hcr (uvrA) with and without rat liver activation at 0 (DMSO), 5, 10, 50, 100, 500, 1000 or 5000 ug/plate, duplicate plates, single trial; toxicity at 5000 ug/plate in several strains. **No evidence of an increase in revertants. Unacceptable** (single trial with only duplicate plates.) Not upgradeable. Gee, 4/12/90.

Chromosome Effects

** 023, 016 070972, 075767, 075764 "KWG 0519: Dominant Lethal Study on Male Mouse to Test for Mutagenic Effects." (Herbold, B., Bayer AG, Institut fur Toxikologie, 11/6/78, Mobay report no. 66746) KWG 0519 [Triadimenol], batch 16001/76, 93.7%; given in a single oral

dose to 50 male NMRI mice per group at 0 (2% Cremophor) or 500 mg/kg, 10 ml/kg; males were mated 1:1 with untreated females for four days per mating, 12 mating periods; dose selection based on a range-finding study to 1000 mg/kg. Document 016, Record No. 075764 contains a report on Endoxan (containing cyclophosphamide), dated 3/30/79, submitted as positive control data with the same strain of male mice and same supplier, same protocol. Record No. 075767 contains information that EPA found the study unacceptable due to lack of dose justification and positive control data. These are included in the several records on file at CDFA. No evidence of a dominant lethal effect with triadimenol. **No adverse effect. Acceptable.** Gee, 4/12/90.

005 014072 Virtual duplicate of 023:070972, however some of the tables in this copy are in German. See one-liner, above.

005 014070 "KWG 0519: Micronucleus Test on Mouse to Evaluate KWG 0519 for Potential Mutagenic Effects." (Herbold, B., Bayer AG, Institut fu"r Toxikologie, Study No. 0519/009, Mobay No. 68785, 8/23/79) KWG 0519 [triadimenol], batch 16010-77, 96.5%; given by oral gavage to NMRI mice, 5/sex/group at 0 (0.5% Cremophor), 350 or 500 mg/kg body weight with two dosings 24 hours apart; sacrificed at 6 hours after the second dosing and polychromatic erythrocytes of the bone marrow analyzed for micronuclei, 1000 PCE's per animal; number of normochromatic erythrocytes per 1000 PCE's also scored. **No evidence of induction of micronuclei. Unacceptable, not upgradeable** (single sacrifice time). Gee, 4/13/90.

005 014071 "KWG 0519: Micronucleus Test on Mouse to Evaluate KWG 0519 for Potential Mutagenic Effects." (Herbold, B., Institut fu"r Toxikologie, Bayer AG, Report No. 7588, Mobay No. 66262, 6/9/78) Triadimenol, KWG 0519, Batch 16001/76, 93.7%; given by oral gavage to 5/sex/group at 0 (0.5% Cremophor), 175 or 350 mg/kg body weight twice; sacrifice at 6 hours after second dosing; 1000 polychromatic erythrocytes scored per animal and normochromatic erythrocytes/1000 PCE's scored; increase in NCE/1000 PCE's at 2 x 350 mg/kg body weight per day. **No evidence of increase in micronuclei formation. Unacceptable, not upgradeable** (single sacrifice time, no dose justification). Gee, 4/13/90.

DNA Damage

** 005 014068 "Evaluation of KWG 0519 in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay." (Litton Bionetics, Inc., Kensington, Maryland, 6/82, LBI Project No. 21001, Mobay No. 82354) KWG 0519, Batch 816 066 128, 97.5%; tested with primary hepatocytes from a single male Fischer 344 rat at 0 (DMSO), 0.25, 0.5, 1.0, 2.5, 10, 25, 50, 100 or 250 ug/ml, 17 hours; unscheduled DNA synthesis by autoradiography. Triplicate coverslips per concentration, scored 50 morphologically normal cells per coverslip for a total of 150 cells per concentration. The test material was toxic at 100 and 250 ug/ml. **No evidence of induction of unscheduled DNA synthesis. Acceptable.** Gee, 4/16/90.

005 014067 "KWG 0519: Triadimenol, the Active Ingredient of Baytan: Study of DNA Damage using the E. coli polA₁⁻ Test." (Herbold, B., Bayer AG, Institut fuer Toxikologie, FRG, Mobay report no. 80212, October 19, 1981) KWG 0519, Batch 816066128, 97.5%; tested with Escherichia

coli strains(K12)p 3478 (pol A₁⁻ and W3110 (pol A⁺); disc diffusion assay at 0 (DMSO), 62.5, 125, 250, 500 or 1000 ug/plate, four replicates per concentration, with and without activation with male Aroclor 1254-induced Sprague-Dawley rat liver S9; chloramphenicol and methylmethane sulfonate controls; no cytotoxicity or differential growth with KWG 0519. **No adverse effect indicated. Unacceptable** ("no test" with no evidence of cytotoxicity, diameter of disc not included, no positive control for activation), not upgradeable. Gee, 4/16/90

005 014073 "KWG 0519: Mutagenicity Test on Bacterial System." (Nagane, M., J. Hatanaka and A. Iyatomi, Nihon Tokushu Noyaku Seizo K. K., Agricultural Chemicals Institute, Toxicological Laboratory, 3/29/82) Bacillus subtilis strains NIG 45 (rec⁻) and NIG 17 (rec⁺) were tested with triadimenol, 97.5%; tested at 200 ug/10 mm. No difference in growth inhibition with KWG 0519 reported. **No adverse effect reported. Unacceptable, not upgradeable** (no justification for concentration used, no activation, single concentration, single plate) Gee, 4/13/90.

006 014080 "Triadimenol Microbial Mutagenicity Study." (Tanahashi, N. and M. Moriya, Department of Toxicology, Institute of Environmental Toxicology, 12/3/82) Triadimenol, 97.5%; tested with Bacillus subtilis strains H17 (rec⁺) and M45 (rec⁻); 0 (DMSO), 50, 100, 200, 500, 1000, 2000, 5000 or 10,000 ug were placed on a 10 mm disk; single sample per concentration, single trial, no activation used; kanamycin as negative control and mitomycin C as positive control; no difference in growth zones with triadimenol. **No adverse effect indicated. Unacceptable, not upgradeable** (single sample, no activation included) Gee, 4/12/90.

Neurotoxicity

Not required at this time.

METABOLISM

Metabolism, Rat

005 014065 "The metabolism of BAYLETONTM-Benzene ring-UL-14C in a rat liver in vitro system". Study was apparently done by Research and Development Department, Mobay Chemical Corp., Dec. 1, 1982. After incubation in liver microsomal fraction, a substantial portion of BAYLETONTM was reduced to triadimenol (one of two isomers of the latter predominated). No other major metabolites were found in this system. Useful information, but not a substitute for metabolism studies employing triadimenol. Aldous, 3/28/90.

005 014066 "Metabolism of BAYLETONTM in rats". Study presumably done by Research and Development Department, Mobay, revised report date, 11/21/79. Single oral doses of 25 mg/kg BAYLETONTM were administered to rats. Label was fairly readily excreted (over 70% in a week). In males, label was distributed 30% in urine and 53% in feces; in females distribution was 40% and 35%, respectively. No activity was found in expired gases. The major identified band in urine and in feces was KWG 0519 acid [formed by oxidation of the isobutyl moiety of triadimenol]. KWG 0519 (two isomers are present) was more abundant in plasma and in liver than the original Bayleton. Prevalence of KWG 0519 isomers was particularly apparent in males. Report is useful information, but not as a substitute for

metabolism studies with triadimenol. Aldous, 3/28/90.

410-215; 117092; "Disposition and Metabolism of [Phenyl-UL- ^{14}C] Triadimefon in Rats" (H.M. Chopade, Agricultural Division, Miles Inc., Stilwell, KS, Study # BLO41801, 7/15/92); nonradiolabeled triadimefon (97.6% purity, [phenyl-UL- ^{14}C] triadimefon (15.78 Ci/mmol, 99.3% radiopurity); single (5 or 50 mg/kg, 5 rats/sex/dose) and multiple oral dosing (5 mg/kg, pretreat 10 rats/sex daily with nonlabeled triadimefon for 14 days prior to pulsing with a single dose of ^{14}C -triadimefon; triadimefon is rapidly absorbed, metabolized and excreted; <1% of the radioactivity was expired as $^{14}\text{CO}_2$ or other volatile organic products; excretion of triadimefon residues in urine and feces was sex dependent; in males, 24-28% of the administered dose was eliminated in urine, and 63-66% in feces, within 96 hrs; in females, 57-67% of the administered radioactivity was excreted in urine, and 32-41% was excreted in the feces, within 96 hrs; total excretion of the administered radioactivity was faster by females: nearly 95% of the dose was excreted by females within 72 hours, whereas males required 96 hrs to reach 90% excretion; no evidence of bioaccumulation after multiple dosing; radioactive residues were highest in the liver and kidneys; four major metabolites, KWG 0519 acid, KWG 1323-gluc, DeMe-KWG-1342-gluc and HO-DeMe-KWG 1342, were identified in urine and five major metabolites including KWG-0519 acid, KWG-1323, KWG-1342, KWG-1323-gluc were detected in feces; unmetabolized parent triadimefon was detected only in male rat feces and only in trace amounts (<1%); **acceptable**; (Leung, 12/4/95).

SUBCHRONIC STUDIES

NOTE: Only the subchronic rat oral (record 014045) and the subchronic rat inhalation (record 014043) were given a separate worksheet. The other "one-liners" reflect reports which have been examined for possible adverse effects and apparent NOEL's. These latter reports were not given exhaustive examinations at this time. Morgan, 7/23/90

003 014045 "KWG 0519: Subchronic toxicity study on rats (Three-month feeding experiment)". Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, June 2, 1977. Dosage groups of 0, 150, 600, and 2400 ppm in diets of Wistar rats. Thirty/sex in controls, and 15/sex in other groups assigned to study. Limited numbers were allocated to specific evaluations (only 5/group were examined histologically, for instance). Apparent NOEL = 600 ppm (slight body weight gain decrements, both sexes; slight decrease in HCT in females; slight but statistically significant ($p < 0.05$) increases in liver weights in both sexes). **No adverse effects indicated. Study is unacceptable** (no ophthalmology, insufficient animals for some parts of the study, and other deficiencies). There is no need for an additional subchronic study at this time, since there is an upgradeable rat chronic feeding study already available. Aldous, 4/11/90.

003 014044; "KWG 0519 Subchronic Toxicity Study on Dogs (Thirteen-week feeding experiment)"; Report 6633; Bayer Ag Institut fur Toxikologie, 2/24/77; Beagle Dogs; 0 (Control), 150, 600 and 2400 ppm; 4/sex/dose level; No mortality occurred; Significant increases were observed between the control and treated groups for alkaline phosphatase ($p < 0.02$, all treated groups), plasma

cholesterol ($p < 0.05$, 600 and 2400 ppm) and N-demethylase activity ($p < 0.01$, 2400 ppm), no gross pathology or histopathology was observed; No adverse effects observed; Apparent NOEL = Apparent NOAEL > 2400 ppm; No CDFA worksheet was completed. Aldous and Morgan, 7/23/90

003 014046; "KWG 0519 Subacute Oral Cumulative Toxicity Study on Rats (Four- week treatment)"; Report 6481; Bayer Ag Institut fur Toxikologie, 11/76; SPF Albino Wistar Rats; 0 (Control), 1.5, 5, 15 and 45 mg/kg/day; 10/sex/dose level; No mortality occurred; No effects were observed among the treated animals; No adverse effects were observed; Apparent NOEL = Apparent NOAEL > 45 mg/kg/day; No CDFA Worksheet was completed. Aldous and Morgan, 7/23/90

034; 112938; "Subacute Toxicity Study of KWG 0519 in Dietary Administration to Rats for 13 Weeks" (Author: N.Nishimura; Laboratory of Safety Evaluation, Gotemba Laboratory, Bozo Research Center Inc., Tokoyo, Japan: Report No. 101939; 12/26/83); KWG 0519 (Lot No. Pt 816171003; 94.0% triadimenol); 0, 120, 600, 3000 ppm in diet; 20 Crj:CD (SD) rats/sex/dose; no mortality or clinical signs due to test article; all 3000 ppm animals showed decreased body weight, hemoglobin, hematocrit, triglycerides, and free fatty acid; high dose females showed increased total cholesterol, phospholipid, total protein and decreased albumin, albumin/ globulin ratios. **Possible adverse effect:** altered liver lipid metabolism with corresponding histopathologic changes in 3000 ppm group; NOEL = 120 ppm(based on liver lipid metabolism); **Acceptable.** (Miller, 7/6/93)

044; 160535; "KWG 0519 Subchronic Toxicity Study in CD-1 Mice (Administration in the Feed Over 13 Weeks)" (Schladt, L. and Sander, E., Bayer AG, Department of Toxicology, Wuppertal, Germany, Bayer AG Report No. 108160, Bayer AG Study No. T0056312, 1/23/98). 821. Triadimenol (KWG 0519) (Batch No. 816176225, purity=97.4%) was admixed to the feed at concentrations of 0, 160, 500, 1500, or 4500 ppm (0, 24.9, 76.8, 235.2, and 872.1 mg/kg/day, respectively, for males and 0, 31.4, 94.1, 296.6, and 797.4 mg/kg/day, respectively, for females) and fed to 10 Crl:CD-1(ICR)BR mice per sex per dose level continuously for a period of 13 weeks. One male at 4500 ppm was found dead on day 4. A statistically significant, persisting decrease in mean body weights was observed in males at 1500 and 4500 ppm and in females at 4500 ppm. Statistically significant increases in alanine aminotransferase, aspartate aminotransferase, and glutamate dehydrogenase levels were observed in males and females at 500, 1500, and 4500 ppm. A statistically significant ($p < 0.01$) and treatment-related increase cytochrome P-450 levels and a statistically significant ($p < 0.01$ for females and $p < 0.05$ for males) and treatment-related increase N-demethylase levels in males and females at all dose levels were observed. A statistically significant increase in mean relative liver weights was observed in males at 4500 ppm and in females at 1500 and 4500 ppm. Microscopic examination revealed treatment-related fat and vacuolation in the liver at all dose levels in females, fat in the liver at all dose levels and vacuolation at 1500 and 4500 ppm in males, dose-related hypertrophy of liver cells in males at 500, 1500, and 4500 ppm and in females at 1500 and 4500 ppm, and dose-related single cell necrosis in liver in males at 4500 ppm and in females at 1500 and 4500 ppm. **No adverse effects.** NOEL = 160 ppm (M: 24.9 mg/kg/day, F: 31.4 mg/kg/day; based on liver adaptation as evident by increased N-demethylase activity and cytochrome P-450 concentration and histopathological changes in the liver. **Unacceptable and not upgradeable** (no ophthalmological examinations were performed on the test animals). (Corlett, 6/10/98)

013 025788; "KWG 0519 Subacute Dermal Toxicity Study on Rabbits"; Report 12496; Bayer Ag Institut fur Toxikologie, 2/29/84; New Zealand Rabbits; 0 (Control), 50 and 250 mg/kg/day for 15 workdays (5 workdays/week), 6 hour exposure/day, 6/sex/dose level (3/sex abraded); vehicle: Cremophor EL/distilled water (5 drops/10 ml formulation); No mortality; mild erythema observed on the abraded sites for all dose levels (including controls), no other treatment-related effects were observed; No adverse effects were observed; Apparent NOEL = Apparent NOAEL > 250 mg/kg/day; No CDFA Worksheet was completed. Morgan, 7/23/90

003 014043 "KWG 0519: Subacute inhalation toxicity study on rats". Bayer AG, Institute of Toxicology, Wuppertal (in-life phase appears to be in-house), Sept. 3, 1976. Wistar II rats (10/sex/group) were exposed to nominal concentrations of 0, 30, 68, and 230 mg/m³ of KWG 0519 for 3 weeks (5 days/week, 6 hr/day). **No treatment effects** were indicated. Study is **not acceptable**: No QA statement, no data confirming actual exposure, no justification of dosages (in the absence of treatment effects and absence of indications that physical limitations prevented more substantive exposure levels). This study type is not currently required (except for tobacco uses), hence unacceptable status of study does not impact product registration. Aldous, 4/12/90.